CASE 4-30096/A

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

ZIMMERMANN ET AL.

APPLICATION NO: 09/463,097

FILED: JANUARY 18, 2000

Art Unit: 1624

Examiner: Emily Bernhardt

FOR: CRYSTAL MODIFICATION OF A N-PHENYL-2-PYRIMIDINEAMINE DERIVATIVE, PROCESSES FOR ITS MANUFACTURE AND ITS USE

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-8, 10 and 12-16, all of the claims under consideration in this application. The Notice of Appeal was mailed on November 5, 2001, making this Appeal Brief due on Monday, January 7, 2002.

(1) Real Party in Interest

The real party in interest is Novartis AG, a Swiss corporation.

(2) Related Appeals and Interferences

Appellants are not aware of any related appeals and interferences.

(3) Status of Claims

Claims 1-8, 10 and 12-16 are pending in this application.

Claims 9 and 11 are cancelled.

Claims 1-8 and 15-16 are rejected under 35 USC 112, second paragraph.

Claim 14 is rejected under 35 USC 112, first paragraph.

Claims 1-8, 10, 13-16 are rejected under 35 USC 102(b) and 35 USC 103(a) over Zimmermann.

Claim 12 is rejected under 35 USC 103(a) over Zimmermann in view of Yu.

The rejection of claims 1-8, 10 and 12-16 is appealed.

(4) Status of Amendments

The Amendment After Final Rejection dated October 3, 2001 is not entered.

(5) Summary of Invention

This invention relates to a crystal modification of the mesylate salt of the pharmaceutical compound, 4-(4-methylpiperazin-1-ylmethyl)-N-{4-methyl-3-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide (represented by the structure of claim 1), hereinafter referred to by its generic name, imatinib mesylate. The invention is based on Appellants' discovery that imatinib mesylate exists in more than one crystal modification. The present claims relate to the non-hydroscopic crystal modification of imatinib mesylate, referred to as the beta crystal modification, as well as to a process for its preparation and to its use as an anti-tumor agent. The beta crystal form of imatinib mesylate is the active ingredient in the commercial drug product, Gleevec™, which has been described as a major breakthrough for the treatment of certain types of cancer.

(6) Issues

I. Whether claims 1-8, 12 and 15-16 conform to the requirements of 35 USC 112, second paragraph?

II. Whether claim 14 conforms to the requirements of 35 USC 112, first paragraph.

III. Whether claims 1-8, 10, 13-16 are properly rejected under 35 USC 102(b) and 35 USC 103(a) over Zimmermann.

IV. Whether claim 12 is properly rejected under 35 USC 103(a) over Zimmermann in view of Yu.

(7) Grouping of Claims

With regard to the claims rejected under 35 USC 112, Appellants request that each of the rejections are argued separately and should be considered separately.

With regard to the art rejections, Appellants believe that the following groups of claims are proper:

(a) Claims 1, 2, 3, 10 and 13 stand or fall together.

(b) Claims 4 and 5 stand or fall together.

(c) Claims 6, 7 and 8 stand or fall together.

(d) Claims 15 and 16 stand or fall together.

(e) Claims 12 and 14 do not fall within the other groups.

(8) Argument

I. Whether claims 1-8 and 15-16 conform to the requirements of 35 USC 112, second paragraph?

(a) Claims 1 and 6, 4-8 and 15 and 16

Claims 1 and 6, 4-8 and 15 and 16 have been rejected under 35 USC 112, second paragraph, based on the Examiner's contention that the claims do not materially differ from one another. No other basis for rejecting these claims under 35 USC 112, second paragraph, is mentioned. Appellants assert that the metes and bounds of these claims are definite to one of skill in the art and, therefore, conform to the requirements of under 35 USC 112, second paragraph.

MPEP 706.03(k) addresses the issue of duplicate claims as follows:

> However, Court decisions have confirmed applicant's right to restate (i.e., by plural claiming) the invention in a reasonable number of ways. Indeed, a mere difference in scope between claims has been held to be enough.

This is not a case where the claims cover the same thing despite a slight difference in wording because each of the rejected claims is of a different scope from the others. Claims 1 and 6 are of different scope from each other because claim 6 requires the crystalline form to show a specific x-ray diffraction characteristic in addition to being non-hydroscopic and crystalline. Claims 4 and 5 differ by the different melting points recited in the claims, and claims 6-8 by the different specific x-ray diffraction requirements. Likewise, claims 15 and 16 define the x-ray diffraction characteristics that must be exhibited by the crystal modification with a different degree of specificity. Clearly, it is possible to infringe any one of these claims without infringing the others. Thus, the claims are of different scope, and the present rejection is improper. For these reasons, Appellants request reversal of the rejection.

(b) Claim 12

With regard to process claim 12, the Examiner questions how the same or overlapping reaction conditions can achieve simultaneously dissolution and digestion. Applicants point out that parts (a) and (b) of claim 12 are alternatives. Therefore, the claim does not require simultaneous

dissolution and digestion. In addition, claim 12 is not limited to any particular solvents. The first paragraph on page 7 of the specification teaches certain solvents that are useful to prepare the crystalline form by digesting another crystal form under the conditions specified in part (a) of claim 12 and other solvents that are useful to prepare the crystalline form by dissolving another crystal form and recrystallizing under the conditions specified in part (b) of claim 12. Thus, claim 12 claims two different alternative processes for making the subject crystalline form. Preparing the subject crystalline form by either of these alternative processes infringes claim 12. Thus, Applicants assert that the metes and bounds of claim 12 are definite to one of skill in the art and that the rejection under 35 USC 112, second paragraph, should be reversed.

In view of the discussion above, Applicants request reversal of all rejections under 35 USC 112, second paragraph.

II. Whether claim 14 conforms to the requirements of 35 USC 112, first paragraph?

Claim 14 is a method of use claim covering the treatment of tumor diseases with the beta crystal modification of imatinib mesylate. The basis for the rejection is the Examiner's assertion that the *in vitro* PDGF inhibition described in the specification is not synonymous with successful treatment of all tumor-related diseases.

In Ex parte Forman, 230 USPQ 546 (BPAI 1986) the Board of Appeals interpreted judicial decisions relating to the enablement requirement to require the specification to contain sufficiently explicit disclosure to enable one having ordinary skill in the art in the relevant field to practice the invention without the exercise of undue experimentation. Appellants assert that the present specification fully meets this standard.

Although the specification describes PDGF receptor kinase inhibition as a property of imatinib, the teaching of this application is not so limited. The specification at pages 10-17 also discloses that imatinib inhibits a number of tyrosine kinases, including PDGF receptor kinase, v-abl kinase, BCR-abl kinase and c-kit receptor kinase, and indicates that the compound is effective for the treatment of tumor conditions that respond to the inhibition of these kinases. Appellants assert that this disclosure provides sufficient guidance to enable one of skill in the art to identify tumor diseases likely to respond to treatment with imatinib without undue experimentation and to treat such tumor diseases with imatinib without undue experimentation. Thus, the present disclosure

enables one of skill in the art to practice the invention of claim 14 and conforms to the requirements of 35 USC 112, first paragraph.

For the reasons discussed above, Appellants request reversal of the rejection of claim 14 under 35 USC 112, first paragraph.

III. Whether claims 1-8, 10, 13-16 are properly rejected under 35 USC 102(b) and 35 USC 103(a) over Zimmermann?

The present claims are limited to a specific crystalline form of imatinib mesylate, and do not claim imatinib mesylate *per se*. Since the disclosure indicates that imatinib mesylate exists in at least two different crystalline forms, only one which is non-hydroscopic under the conditions set forth in the claims and/or shows the specified characteristics in the x-ray diffraction pattern, if issued, the present claims would not prevent a third party from making, using and selling what the Examiner asserts is anticipated by Zimmermann - the mesylate salt of the subject compound. Such claims only prevent the making, using and selling (etc.) of the claimed crystalline form. Clearly, there is a distinction between claims covering a mesylate salt of a compound and a particular crystalline form of that mesylate salt. However, Appellants assert that even the mesylate salt *per se* is not anticipated by Zimmermann.

The Examiner appears to agree that while Zimmermann specifically discloses imatinib, the mesylate salt is not prepared in the reference. The disclosure of Zimmermann includes a generic disclosure of numerous potential salt forms at column 3, lines 22-43, which is not specific to imatinib, but applies to all of the disclosed compounds. For the rejection, this generic disclosure is apparently combined with claim 23, which claims imatinib and pharmaceutically acceptable salts thereof, but does not mention any specific salt.

In making the present rejection, the Examiner cites In re Petering and Fall, 133 USPQ 275 (CCPA 1962) and In re Schaumann, Bartsch, Roesch, Guthlein, and Braun, 197 USPQ 5 (CCPA 1978) as the basis for asserting that anticipation is proper even though the reference does not actually prepare the mesylate salt of imatinib. Additionally, the Examiner cites In re Best, Bolton and Shaw, 195 USPQ 430 (CCPA 1977), In re Fitzgerald, Sanders, and Bagheri 205 USPQ 594 (CCPA 1980) and In re Grose and Flanigen, 201 USPQ 57 (CCPA 1979) as the basis for asserting that the claimed crystal modification is inherently disclosed by the reference. The Examiner relies

on this case law to contend that it is Applicants' burden to show that the claimed crystalline form cannot be made following routine conditions.

By relying on In re Petering and In re Schaumann, the Examiner asserts that Zimmermann's disclosure at column 3 is sufficiently specific to lead one of skill in the art to immediately envision a narrow genus of compounds which includes the mesylate salt of the present compound. However, the situation in Petering and Schaumann are readily distinguishable from the present situation because each considered whether the reference taught a *pattern of preferences* with sufficient specificity to lead the skilled artisan to immediately envision a narrow genus of compounds that included the claimed compound. In contrast, Zimmermann does not teach a preference for salt forms of the present compound and the disclosure at column 3 does not provide any direction as to which of the salt forms of the present compound might be preferred. In particular, it contains no specific disclosure that would lead one skilled in the art to select the mesylate salt, or even the aliphatic sulfonic acid salts, of the present compound from the myriad of possibilities. Moreover, there is no indication in the reference that any salt of the present compound was actually prepared, whereas in the cited cases a substantial number of the compounds in the narrow genus were specifically disclosed. Therefore, the present claims are not properly rejected over Zimmermann based on the holding of In re Petering and/or In re Schaumann

Moreover, Appellants again emphasize that the present application does not claim imatinib mesylate, *per se*, but instead claims only a specific crystal modification of imatinib mesylate. Even if Zimmermann contained sufficient disclosure to anticipate imatinib mesylate, it has no disclosure which would lead one to expect that the compound exists in more than one crystal form, and therefore contains no disclosure that anticipates or renders obvious the claimed crystal modification.

In addition, and in contrast to the statements made by the Examiner to justify the rejection, the disclosure in column 3 of Zimmermann comprises far more than 32 salts. The reference states that compounds having at least one basic group may form acid addition salts, for example with inorganic acids, or with suitable organic carboxylic or phosphonic acids. These are broad generic terms which are further defined by subgeneric definitions, like "a phosphoric acid" (i.e. clearly not restricted H_3PO_4 , but also encompassing other phosphoric acids), "aliphatic mono- or di-carboxylic acids", "amino acids", "aromatic carboxylic acids", "aromatic-aliphatic carboxylic acids", "heteroaromatic carboxylic acids", "aliphatic sulfonic acids", "aromatic sulfonic acids", thus clearly comprising a huge number of possible acid addition salts. The 32 salts alluded to by the Examiner

are merely exemplifications of the acids within the diverse generic and subgeneric terms. Applicants further point out that column 3, lines 42-43, of Zimmermann states that mono- and poly-acid addition salts may be formed when several basic groups are present. The compound of the present formula I clearly contains several basic groups, e.g. the piperazinyl and pyridyl moieties, and, hence, could form such poly-acid addition salts according to Zimmermann.

In response to the Examiner's reliance on In re Best and In re Fitzgerald these cases are distinguishable from the present circumstances because both cases relate to instances where the patent applicant was unable to satisfactorily differentiate the claimed product from the product actually made in the prior art. In the present case, since imatinib mesylate was not actually made in the reference, there is no prior art form of imatinib mesylate from which the claimed crystalline form needs to be differentiated.

In re Grose is also based on the patent applicant's failure to present sufficient evidence to demonstrate that the claimed zeolite was different from a zeolite actually made in the prior art. See, page 63:

> "The present record does not support the conclusion that appellants' zeolite and Milton's zeolite R are zeolites having different crystal structures. The admitted permissible variations in the diffraction data of appellants' zeolite would embrace, at least prima facie, the diffraction data disclosed for Milton's zeoliteR. Thus, this is not a situation where the difference in diffraction pattern could only be attributed to a difference in crystal structure."

Applicants further point out that the Grose opinion is consistent with Glaxo v. Novopharm 34 USPQ2d 1565 (Fed. Cir. 1995) ("Glaxo"), which is discussed below, because the CCPA clearly indicates that claimed zeolite would have been patentable if the patent applicant had satisfactorily demonstrated that the claimed zeolite had a different crystal structure from Milton's. See, 201 USPQ page 64 where the CCPA cites In re Cofer, 148 USPQ 268, 271 (CCPA 1966) to indicate that after finding the claimed zeolite different from the prior art, the Board improperly rejected the claims for obviousness because an obviousness determination requires consideration of whether the prior art suggests the particular structure or form of the composition as well as methods for obtaining that structure or form. In the present case, the prior art does not suggest any particular form of imatinib mesylate or suggest that any particular form could be made by a particular method. Thus, the Grose opinion also supports Applicants' position that the inventive crysalline form of imatinib mesylate is not anticipated by or obvious over the disclosure of Zimmermann.

Applicants further assert that the Examiner's position is not consistent with the holding in Glaxo, cited above. In Glaxo, a case with factual circumstances similar to the present facts, the Federal Circuit held that for the prior art to inherently anticipate a claim directed to a crystalline form of a compound, the reference must contain disclosure that would invariably produce the claimed crystal form when followed by one of skill in the art.

The Glaxo case related to U.S. Patent No. 4,521,431 with claims to a crystal form of a drug substance, the crystal form of ranitidine hydrochloride designated Form 2. U.S. Patent No. 4,128,658, the prior art, specifically disclosed ranitidine hydrochloride and a process for preparing it in Example 32. During prosecution, the patent applicant asserted that Example 32 of the '658 patent yielded Form 1 ranitidine hydrochloride and provided evidence that the claimed Form 2 ranitidine hydrochloride different from the prior art Form 1 ranitidine hydrochloride in order to gain allowance of the claims.

The district court held that the evidence demonstrated that both the Form 1 and Form 2 crystal forms could be prepared by following the disclosure of Example 32 of the '658 patent. Based on this factual determination, District Court held, and the Federal Circuit affirmed, that the '658 patent did not inherently anticipate a patent claim directed to Form 2 ranitidine hydrochloride because one of skill in the art following Example 32 did not inevitably produce the Form 2 polymorph (i.e. because either Form 1 or Form 2 could be made). The fact that the skilled artisan **could** produce Form 2 ranitidine hydrochloride by following the teaching of the reference was not sufficient to render invalid a composition of matter claim to Form 2 ranitidine hydrochloride. Thus, according to Glaxo, an inherent anticipation is proper only in circumstances where the claimed subject matter is inevitably produced by following the teaching of the reference.

In the present instance, Zimmermann does not disclose any specific procedure for preparing imatinib mesylate. It merely suggests that numerous salts of the disclosed compounds, incuding mesylate salts, could be prepared. Moreover, the Examiner has not even alleged that anything in the reference leads the skilled artisan to expect that imatinib mesylate would exist in more than one crystal form when it was actually made. Because the presently claimed crystalline form is not the inevitable result of following the teaching of Zimmermann and because nothing in Zimmermann suggests that imatinab mesylate would exist in more than one crystal form, Applicants assert, in accordance with the Glaxo decision, that Zimmermann does not render claims to a crystalline form of imatinib mesylate unpatentable under either of 35 USC 102 or 103.

Appellants further assert that the Examiner's reliance on Petering is inconsistent with the Glaxo case cited above. Glaxo held that a crystal form of ranitidine hydrochloride was patentable over a different crystal form of the same compound. If the disclosure of the exact salt, ranitidine hydrochloride, did not anticipate other crystal forms of the same salt that could be made by the same process, Applicants do not understand how the Zimmermann reference can be properly relied upon as anticipating undisclosed crystal forms of a salt that is not even prepared in the reference.

Claims 1, 2, 3 and 13 of present application claim the inventive crystal form, and claim 10 claims pharmaceutical compositions of the inventive crystal form, based on its property of being non-hydroscopic. Nothing in Zimmermann suggests that imatinib mesylate would exist in hydroscopic and non-hydroscopic forms. Therefore, claims 1, 2, 3, 10 and 13 are patentable over Zimmermann.

In addition to requiring that the crystalline imatinib mesylate be non-hydroscopic, claims 4 and 5 require the crystalline material to be 99% by weight of the beta crystal modification and have specific melting point characteristics. Since nothing in the reference even suggests that there would be different crystal modifications having different melting point characteristics, claims 4 and 5 are further distinguished from the disclosure of the reference.

In addition to requiring that the crystalline imatinib mesylate be non-hydroscopic, claims 6, 7and 8 require the crystalline imatinib mesylate to show specific x-ray diffraction characteristics. Since nothing in the reference suggests anything about the characteristics of the unit cells of crystalline imatinib mesylate, requiring x-ray diffraction characteristics further distinguishes claims 6, 7 and 8 from the reference.

Claim 14 covers the use of the inventive crystal form to treat tumor diseases. The patentability of this claim depends on the patentability of the beta crystal modification.

Claims 15 and 16 claim the beta crystal modification of imatinib mesylate based on its x-ray diffraction characteristics. Since the alpha and beta crystal modifications of imatinib mesylate are distinguished by their x-ray diffraction patterns in addition to their hydroscopicity properties, claims 15 and 16 distinguish the claimed crystal modification from the alpha crystal modification. Since nothing in the reference suggests anything about the characteristics of the unit cells of crystalline imatinib mesylate, describing the claimed crystal modification by its x-ray diffraction characteristics distinguishes the claims from the disclosure of the reference.

For the reasons discussed above, Appellants request reversal of the rejection of claims 1-8, 10 and 13-16 under 35 USC 102(b) and 35 USC 103(a) over Zimmermann

IV. Whether claim 12 is properly rejected under 35 USC 103(a) over Zimmermann in view of Yu?

Claim 12 was rejected under 35 USC 103(a) over the combined teachings of Zimmerman and Yu. Claim 12 covers a process for the preparation of the inventive beta crystal modification.

First, Applicants assert that claim 12 is patentable because the desired end product is novel and unobvious for the reasons discussed above.

In addition, with respect to the specific process conditions required by claim 12, a person skilled in the art would have been completely unaware under which conditions the beta modification is formed instead of, *inter alia,* the alpha modification. Yu is applied to show that polymorphic forms are frequently encountered for pharmaceuticals and that the desired form can often be obtained a number of ways including the dissolution of other forms in various solvents including methanol. See. Office action of September 28, 2000, page 4. However, such a disclosure does not teach the skilled artisan how to make the beta crystal modification of imatinib mesylate. Therefore, Yu does not remedy the deficiencies of the primary reference. Accordingly, Appellants assert that the process of claim 12 is patentable over the combined disclosure of the references.

Reversal of the rejection of claim 12 is requested for the reasons discussed above.

Conclusion

The various rejections are improper and should be reversed. Therefore, Appellants request reversal of the rejection of claims 1-8, 10 and 12-16.

Respectfully submitted,

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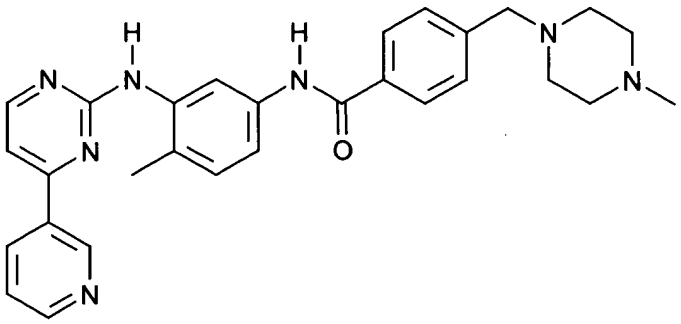
Appendix – Claims on Appeal

1. A crystalline form of the monomethanesulfonic acid addition salt of a compound of formula I,



(I)

which is non-hygroscopic in a glass climatic chamber at 25 °C and relative humidities up to and including 93%.

2. A crystalline form according to claim 1 of the methanesulfonic acid addition salt of a compound of formula I, which comprises at least 95% by weight crystals of the β-modification and remains dry at 93% relative humidity and 25°C.

3. A crystalline form according to claim 1 of the methanesulfonic acid addition salt of a compound of formula I, which comprises at least 99% by weight crystals of the β-modification and remains dry at 93% relative humidity and 25°C.

4. A crystalline form according to claim 1 of the methanesulfonic acid addition salt of a compound of formula I, which comprises at least 99% by weight crystals of the β-modification and has a melting point below 225°C.

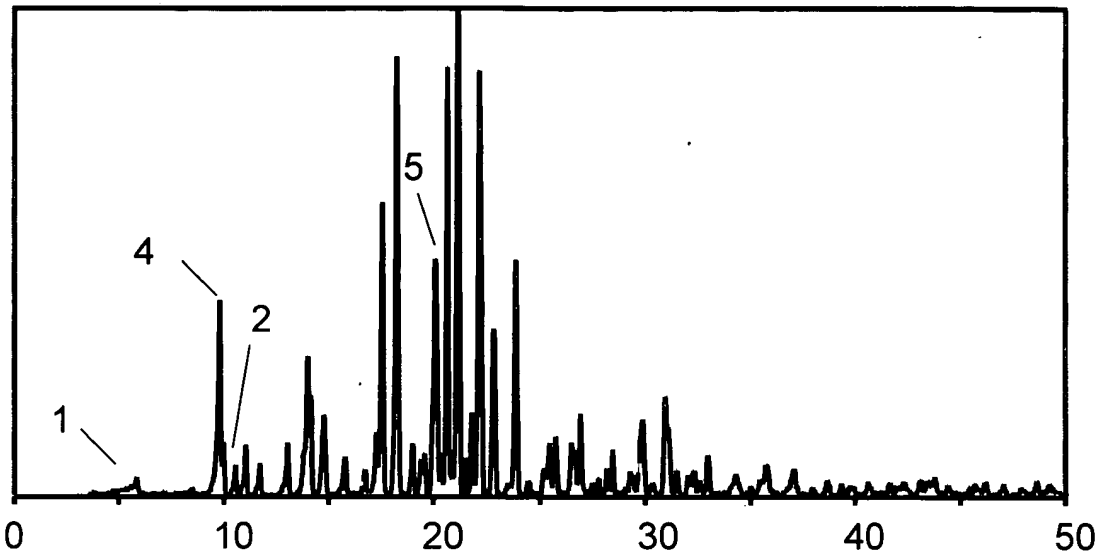
5. A crystalline form according to claim 1 of the methanesulfonic acid addition salt of a compound of formula I, which comprises at least 99% by weight crystals of the β-modification and has a melting point of less than 217°C, defined as the start of melting in the differential scanning calorimetry thermogram.

6. A crystalline form according to claim 1 of the methanesulfonic acid addition salt of a compound of formula I, which shows on X-ray diffraction a peak at an angle of refraction 2theta of 20°, said peak having a relative line intensity of about 65 as compared to the most intense line in the diagram.

7. A crystalline form according to claim 3 of the methanesulfonic acid addition salt of a compound of formula I, which shows in an X-ray diffraction diagram lines having a relative line intensity, as compared to the most intense line in the diagram, of about 20 or more at the following angles of refraction 2theta : 9.7°, 13.9° , 14.7°, 17.5°, 18.2°, 20.0°, 20.6°, 21.1°, 22.1°, 22.7°, 23.8°, 29.8° and 30.8°.

8. A crystalline form according to claim 5 of the methanesulfonic acid addition salt of a compound of formula I, which has a melting point of about 217°C, defined as the start of melting in the differential scanning calorimetry diagram, and which shows essentially the following X-ray

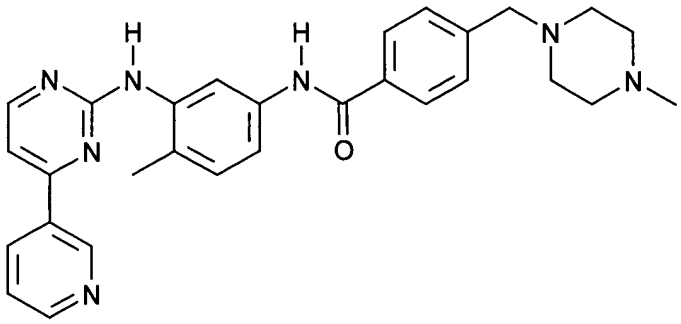
diffraction diagram:



wherein the angle of refraction, 2 theta, is plotted on the horizontal axis and the relative line intensity on the vertical axis.

10. A pharmaceutical composition, comprising the β-crystal form according to claim 1 of the methanesulfonic acid addition salt of a compound of formula I and a pharmceutically acceptable carrier.

12. A process for the preparation of the β-crystal form of the methanesulfonic acid addition salt of a compound of formula I



which comprises

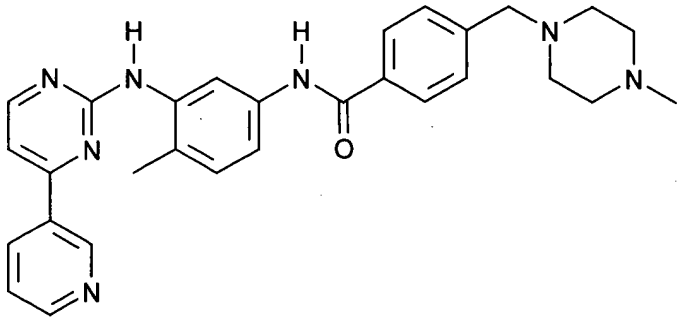
a) digesting another crystal form or an amorphous starting material of the methanesulfonic acid addition salt of a compound of formula I with a suitable polar solvent in suspension at a temperature between 20 and 50°C, or

b) dissolving another crystal form or an amorphous starting material of the methanesulfonic acid addition salt of a compound of formula I, in a polar solvent at a suitable temperature of 25°C up to

the reflux temperature of the reaction mixture, and then initiating crystallisation by adding a small amount of the β-crystal form as seed crystal at a temperature between 20 and 70°C.

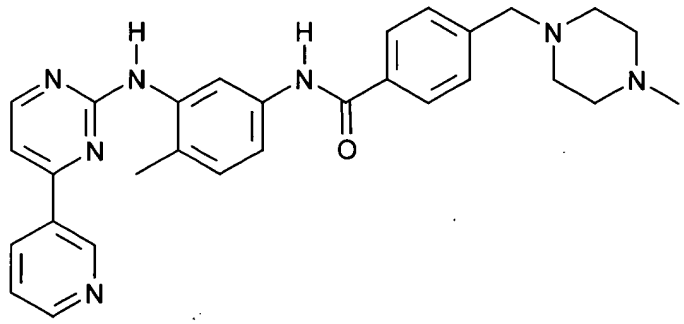
13. A crystalline form according to claim 1 of the methanesulfonic acid addition salt of a compound of formula I, which comprises at least 90% by weight crystals of the β-modification and remains dry at 93% relative humidity and 25°C.

14. A method for treating a tumor disease in a patient, which comprises administering to the patient an effective amount of a compound of the formula



in its β-crystal modification.

15. A crystalline form of the methanesulfonic acid addition salt of a compound of formula



which displays x-ray diffraction peaks at 9.7° and 20.0° 2 theta.

16. A crystalline form of claim 15 which displays x-ray diffraction peaks having a relative line intensity, as compared to the most intense line in the diagram, of about 20 or more at the following angles of refraction 2 theta : 9.7°, 13.9° , 14.7°, 17.5°, 18.2°, 20.0°, 20.6°, 21.1°, 22.1°, 22.7°, 23.8°, 29.8° and 30.8°.